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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PREVENTION, PESTICIDES, AND TOXIC SUBSTANCES
WASHINGTON, D.C. 20460

August 17, 2004

MEMORANDUM:

SUBJECT: Human Health Risk Assessment for Fluridone TRED
PC Code 112900. DP Barcode D306456.

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Please find attached the Human Health Risk Assessment for the fluridone Tolerance Registration Eligibility Decision (TRED). This assessment is based upon the Toxicology Chapter (TXR 0052046) and the Dietary Exposure Assessment Memorandum (D299947). Information was also drawn from the EFED's Drinking Water Assessment (D300012).

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1.0 EXECUTIVE SUMMARY

Overall Summary

The Health Effects Division (HED) has conducted a human health risk assessment for the active ingredient **Fluridone** for the Tolerance Registration Eligibility Decision (TRED). HED determined that the currently available data are adequate to support the TRED. The food, drinking water and recreational swimmer risks are not of concern either separately or when aggregated.

Introduction

Fluridone is a systemic herbicide that is used to manage aquatic weeds in ponds and lakes. It is particularly useful for the control of hydrilla in the southern states and eurasian milfoil in the northern states. It inhibits carotene synthesis which causes the loss of chlorophyll. It is typically applied to the whole water body because it requires a contact time of 45 days to be effective. The labels permit single treatments of up to 90 ppb for whole lake treatments and 150 ppb for partial lake treatments, with a maximum cumulative application of 150 ppb per growth cycle. There are no direct food uses for fluridone, however, water from areas treated with fluridone can be used for the irrigation of crops and pastures.

Toxicology of Fluridone

The acute toxicity of fluridone is moderate to low and it is not a skin sensitizer.

In subchronic dietary feeding studies, fluridone caused increased incidence of liver hypertrophy in mice and no effects in dogs at 200 mg/kg/day, the highest doses tested.

In developmental toxicity studies, maternal toxicity (abortions and decreased body weight and food consumption) were seen in rabbits at 300 mg/kg/day or above. In the rats, maternal toxicity(decreased body weight gains and food consumption) were seen at 300 mg/kg/day. Developmental toxicity such as decreased fetal weight, increased incidences of rudimentary ribs. and delayed ossification in sternebrae and pelvic girdle were seen at 1000 mg/kg/day.

In a 3-generation reproduction study in rats, no maternal toxicity was seen at any dose levels. Also, the test chemical did not significantly affect any of the reproductive parameters. For the offspring, there was a increased pup weight on lactation day 21 at 112 mg/kg/day.

In the combined chronic toxicity/carcinogenicity study in rats, chronic toxicity consisted of decreased body weights, decreased eosinophil counts and decreased absolute and relative liver and kidney weights at 81 mg/kg/day In addition, fluridone at 81 mg/kg/day also caused an increased incidence of small testes, ocular keratitis and pale or granular kidneys. In a chronic toxicity study in dogs, significant increases in absolute liver weights and increases in alkaline phosphatase activity in female dogs were seen at the highest dose-tested (400 mg/kg/day).

No neurotoxicity was reported in any of the studies.

Mutagenicity and Cancer

Fluridone was negative for inducing mutations in all guideline studies of the standard battery of mutagenicity tests.

In the combined chronic toxicity/carcinogenicity study in rats, there was no treatment-related increase in tumor incidence in any treated groups when compared to controls. The Carcinogenicity study in mice showed no treatment-related increase in tumor incidence in any treated groups when compared to controls. Increase in alkaline phosphatase activity and increased incidence of hepatocellular hyperplasia were seen at 50 mg/kg/day.

The HED Cancer Assessment Review Committee evaluated the available data and concluded that the data did not provide evidence for the carcinogenicity of fluridone in either rats or mice.

Dose Response and Endpoint Selection for Fluridone

The following endpoints were used for fluridone risk assessment:

- A developmental NOAEL of 125 mg/kg/day was selected from a developmental toxicity study in rabbits in which increased incidences of abortions were observed at the LOAEL of 300 mg/kg/day. This NOAEL was selected for acute dietary exposures of adult females of reproductive age.

- A NOAEL of 15 mg/kg/day was selected from a 2 yr carcinogenicity study in mice in which increased alkaline phosphatase activity and hepatocellular hyperplasia was observed at the LOAEL of 50 mg/kg/day. This NOAEL is applicable to chronic dietary exposures as well as short and intermediate term dermal, inhalation and incidental oral exposures.

- A dermal absorption factor of 39 percent was selected for converting dermal exposures to oral equivalent doses.

The target Margin of Exposure (MOE) for both occupational and residential populations is 100, which includes the standard safety factors of 10X for intraspecies variability (i.e. differences among humans) and 10X for interspecies variability (differences between humans and animals). Addtional factors for database uncertainties were not required because the database was considered complete and no datagaps were identified.

The FQPA Safety Factor is 1X based upon the available hazard and exposure data and is applicable to all population subgroups and exposure scenarios. There was no evidence of pre- or post-natal susceptibility from *in utero* or postnatal exposure to fluridone. There are no residual uncertainties.

Toxicology of N-Methyl Formamide

N-methyl Formamide (NMF) is the most toxic and prevalent o the fluridone metabolites and degradates. It is formed in water by the photolysis of fluridon . The toxicology database for NMF is limited to one developmental study that was reported i n the literature. This study indicated that NMF causes skeletal malformations in both rats nd rabbits with NOAEL of 10 mg/kg/day. NMF is not a metabolite in foods.

Dietary Risk

Dietary risks for fluridone were calculated at the tier 1 level by using tolerance level residues and the assumption that100 percent of the crop would be irrigated with fluridone containing water. Acute dietary risk estimates were calculated only for females o child-bearing age, as no endpoint was identified for the other populations. At the 95th percentile of exposure, the acute dietary exposure estimates are less than 1% of the aPAD, which mean that the risks are below the HED's level of concern (100% aPAD). The chronic risks wer calculated for all of the populations and were also well below HED's level of concern. These risks ranged from 1% of the cPAD for the U.S. population to 3.6 % of the cPAD for chi dren aged 1 to 2. Dietary risks for NMF were not calculated because NMF is not a metabolite in foods.

Drinking Water Risks

The drinking water risks were calculated for both fluridone and NMF because fluridone degrades to NMF in water. The fluridone labels permit applications of u to 20 ppb at potable water intakes and requires that applications of greater than 20 ppb m st be further than 1/4 mile from potable water intakes. Given this label restriction it can be ass med that the fluridone EEC for drinking water drawn from lakes would be 20 ppb or less. The EECs for NMF were derived from the fluridone EECs by assuming a fluridone to NMF con ersion efficiency of 74% and by adjusting for the ratio of the NMF and fluridone molecular wei hts. Given the above assumptions a fluridone concentration of 20 ug/liter will yield n NMF concentration of 2.64 ug/liter. These concentrations were used along standard assu ptions of body weight and daily water consumption to calculate MOEs for both fluridone and NMF. All the MOEs exceeded the target MOE of 100 by one or more orders of magnitude.

Recreational Swimmer Risks

These exposures were evaluated using the SWIMODEL and st ndard assumptions from the residential SOPs. Acute, short term and intermediate term exp sures were evaluated for fluridone and acute and short term exposures were evaluated fo NMF. The maximum label target concentration of 150 ppb was used assess fluridone expo ures. The corresponding NMF concentration of 20 ppb was based upon the fluridone to NMF conversion efficiency of 74% as cited by EFED. All of the MOEs for both fluridone and NMF exceed the target MOE of 100 by one or more orders of magnitude.

Aggregate Risks

The aggregate risk for fluridone were calculated by combining the food, drinking water and swimmer exposures while the aggregate risks for NMF were calculated by combining drinking water and swimmer exposures. All of the aggregate MOEs for both fluridone and NMF exceed the target MOE of 100 by one or more orders of magnitude which means that the aggregate risks are not of concern.

Risk Characterization

This risk assessment was based upon the assumption that maximum label rates would be used. Literature data and discussions with the aquatic plant management community have indicated, however, that actual use rates are in the range of 10 to 20 ppb due to the high cost of fluridone and it's proven efficacy at these lower rates. Therefore, risks values provided in this risk assessment are bounding estimates.

Data Requirements

There are no data requirement for fluridone.

Tolerance Reassessment

All of the existing fluridone tolerances established at 40 CFR 180.420 are adequately supported. These tolerances are listed in Table 1.

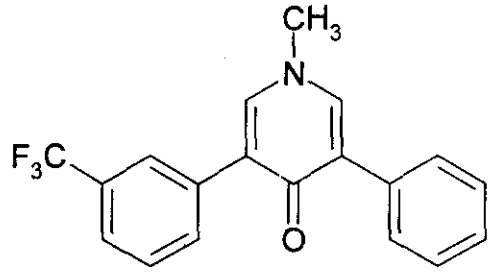
Table 1. List of Tolerances for Fluridone Included in the Dietary Risk Assessments			
Commodity	Tolerance (ppm)	Commodity	Tolerance (ppm)
Avocado	0.1	Hog, Meat by-products	0.05
Cattle, Fat	0.05	Hops	0.1
Cattle, Kidney	0.1	Horse, Fat	0.05
Cattle, Liver	0.1	Horse, Kidney	0.1
Cattle, Meat, except Kidney and Liver	0.05	Horse, Liver	0.1
Cattle, Meat by-products	0.05	Horse, Meat, except Kidney and Liver	0.05
Citrus	0.1	Horse, Meat by-products	0.05
Cotton, Undelinted Seed	0.1	Leafy vegetables	0.1
Crayfish	0.5	Legume, forage	0.15
Cucurbit vegetables group	0.1	Milk	0.05
Egg	0.05	Nut	0.1
Fish	0.5	Poultry, Fat	0.05
Fruit, Pome	0.1	Poultry, Kidney	0.01
Fruit, Stone	0.1	Poultry, Liver	0.01
Goat, Fat	0.05	Poultry, Meat, except Kidney and Liver	0.05
Goat, Kidney	0.1	Poultry, Meat by-products	0.05
Goat, Liver	0.1	Root Crop Vegetables	0.1
Goat, Meat, except Kidney and Liver	0.05	Seed and Pod Vegetables	0.1
Goat, Meat by-products	0.05	Sheep, Fat	0.05
Grain, crop	0.1	Sheep, Kidney	0.1
Grass, Forage	0.15	Sheep, Liver	0.1
Hog, Fat	0.05	Sheep, Meat, except Kidney and Liver	0.05
Hog, Kidney	0.1	Sheep, Meat by-products	0.05
Hog, Liver	0.1	Small Fruit	0.1
Hog, Meat, except Kidney and Liver	0.05	Vegetables, fruiting	0.1

2.0 Ingredient Profile

Chemical Structure and Identification

Fluridone {1-methyl-3-phenyl-5-[3-(trifluoromethyl)phenyl]-4(1H)-pyridinone} is a pyridazone herbicide registered for use on aquatic weeds in lakes, ponds and canals. The chemical structure of fluridone and identifying information is included below:

Empirical Formula: $C_{19}H_{14}F_3NO$
Molecular Weight: 329.3
CAS Registry No.: 59756-60-4
PC Code: 112900



Physical Properties of Fluridone

Fluridone is an off-white crystalline solid with a melting point of 154-155° C and a bulk density of 1.4 g/cm^3 (pyconometer method). It has a log octanol/water partition coefficient of 1.87 and a vapor pressure of $<1 \times 10^{-7}$ mm hg at 25° C. Fluridone in the environment is not particularly persistent or mobile (Kd range from 5.56 to 70.3 ml/gram). Fluridone is minimally soluble in water (12 ppm) and soluble in organic solvents (0.5 to >10 mg/ml).

Summary of Registered Uses

Fluridone is a systemic herbicide that is used to manage aquatic weeds in ponds and lakes. It is particularly useful for the control of eurasian milfoil in the northern tier states and for hydrilla in the southern states. It inhibits carotene synthesis which causes the loss of chlorophyll. It is typically applied to the whole water body because it requires a contact time of 45 days to be effective. The labels permit single treatments of up to 90 ppb for whole lake treatments and 150 ppb for partial lake treatments, with a maximum cumulative application of 150 ppb per growth cycle. If the treatment area is within 1/4 mile of a water intake, the fluridone concentration must be maintained below 20 ppb.

The registered fluridone products are listed in Table 2.

Table 2 - Active Registrations for Fluridone as of 6/01/04				
Product	**Formulation**	**Reg Number**	**Company Name**	**% of Active Ingredient**
Fluridone Technical		1812-426	Griffin L.L.C.	99.2
Fluridone SC	Liquid Concentrate	1812-435	Griffin L.L.C.	41.7
Fluridone SRP	Granular	1812-447	Griffin L.L.C.	5
Sonar Technical		67690-4	SePRO Corporation	99.2
Sonar SRP/5P	Granular	67690-3	SePRO Corporation	5
Sonar A.S.	Liquid Concentrate	67690-3	SePRO Corporation	41.7
Sonar X	Granular	67690-3	SePRO Corporation	5
Sonar* Q Quick Release	Granular	67690-3	SePRO Corporation	5

3.0 Metabolism Assessment

Metabolism Profile in Rats/Humans

In a metabolism study in rats, fluridone was rapidly and almost completely absorbed into the systemic circulation and eliminated in both the male and female rats within 3 days. The total radioactivity recovered within 3 days after dosing in the urine and feces were 78-90% and 87-97% of administered dose in males and females, respectively. The majority (approximately 70%) of the radioactivity was eliminated via feces. No tissue accumulation was observed. The major components in the feces were fluridone and fluridone metabolites produced primarily by ring hydroxylation and N-demethylation.

Nature of the Residue in Foods

Fluridone is not applied directly to crops. However, residues of fluridone may get into the U.S. food supply when water from treated ponds or lakes is used to water crops. Fluridone residues could end up in livestock commodities if livestock drink water that has been treated with fluridone or if livestock consume crops that have been irrigated with fluridone-treated water.

Studies have been conducted to determine if fluridone is transformed when it is applied to crops in irrigation or if residues are consumed by livestock. Fluridone, ^{14}C-labeled in the 4-position of the pyridinone ring, was used in irrigated crop metabolism studies conducted on grapefruit, corn, soybeans, lettuce, and alfalfa. All applications were foliar applications at a rate of 4 acre-inches of water containing fluridone at a concentration of 123 ppb. In addition, soil applications were conducted with corn and alfalfa. Greater than 73% of the residue in all crops was identified as the parent compound, fluridone. This chemical has never been reviewed by the Metabolism Committee. The risk assessment team has reviewed the applicable studies and has determined

that if finite residues are present, fluridone is the most likely species present.

Livestock metabolism studies have been conducted with cattle, swine, and chickens. All studies have shown considerable metabolism of the parent compound with subsequent incorporation into the livestock tissues. Fluridone and its 4-hydroxy metabolite were found in cattle and swine liver at levels less than 4% each of the total radioactive residue (TRR) for cattle, and 0.5% each for swine. No attempt was made to identify the TRR in poultry, due to low levels. Given the relatively low dietary burden of fluridone, and the extensive metabolism of fluridone and the low residues expected in edible commodities, the risk assessment team has concluded that the residue of concern for risk assessment and tolerance-setting purposes is the parent, fluridone.

Environmental Degradation

As discussed in the EFED Drinking Water Assessment (D300012 of 4/1/04) N-methyl formamide (NMF) is the major degradate of fluridone when fluridone is applied to water bodies. The maximum daily conversion efficiency of 74% of the applied fluridone was observed in an aquatic photolysis study (MRID 419401-04) that was conducted under laboratory conditions using distilled water. A limited number of studies have been conducted under field conditions and these studies suggest that NMF is generally undetectable in water bodies treated with fluridone at the maximum application rate. In one study, NMF was not detected (LOD = 2 ppb) in any of the 192 water samples collected following the application of fluridone to two ponds in Florida. Ponds were used in this study instead of lakes or canals to maximize the concentration and persistence of fluridone and NMF.

Summary of Metabolites and Degradates

A summary listing of the metabolites and degradates of fluridone is included in Appendix A.

Toxicity Profile of Major Metabolites and Degradates

NMF is the most toxic and prevalent of the fluridone metabolites and degradates. The toxicology database for NMF is limited to one developmental study that was reported in the literature. This study indicated that NMF causes skeletal malformations in both rats and rabbits with NOAEL of 10 mg/kg/day. The results of this study are summarized in Table 3.

Table 3 - Toxicology Profile of NMF			
STUDY* - DOSE LEVELS	**NOAEL mg/kg/day**	**LOAEL mg/kg/day**	**EFFECTS**
Developmental toxicity–**rats** 0, 1, 5, 10, or 75 mg/kg/day by gavage	maternal 10 developmental 10	maternal 75 developmental 75	decreased body weight gain and food consumption decreased fetal viability; decreased fetal weight; significant increase in the incidence of malformations including cephalocele and sternoschisis; increased incidence of incomplete ossification of various skeletal structures
Developmental toxicity–**rabbits** 0, 5, 10, or 50 mg/kg/day by gavage	maternal 10 developmental 10	maternal 50 developmental 50	decreased body weight gain and food consumption decreased fetal viability; decreased fetal weight; malformations including gastroschisis, cephalocele, domed head, flexed paw, and skull and sternum anomalies.
*Fundamental and Applied Toxicology **27 (2)**, 239-246, 1995.			

Metabolites/Degradates Included in the Risk Assessment and Tolerance Expression

A summary of the fluridone metabolites and degradates included in the risk assessment and tolerance expression is included in Table 4. No major plant metabolites were found in the irrigated crop study, so only the parent compound is included. Extensive metabolism of the low total residues were found in the ruminant, poultry, and swine metabolism studies, so no major degradates were identified. Fluridone and 4-hydroxyfluridone are the major degradates in fish and are assumed to have approximately equivalent toxicity, so both are included in the risk assessment and tolerance expression. Benzoic acid and its 3-trifluoromethyl benzoic acid are aqueous photolysis products found in laboratory studies conducted with lake water. Although it would not have a toxicity profile similar to the parent, there is not a concern for adverse health effects at the levels found as a result of fluridone applications. Finally, another aqueous photoproduct found in laboratory studies, N-methylformamide (NMF), is more toxic than the parent compound and requires a separate assessment.

Table 4 - Metabolites/Degradates Included in the Risk Assessment and Tolerance Expression			
Matrix		**Residues included in Risk Assessment**	**Residues included in Tolerance Expression**
Plants	Irrigated Crops	Fluridone	Fluridone
	Rotational Crop	N/A	N/A
Livestock	Ruminant	Fluridone	Fluridone
	Poultry	Fluridone	Fluridone
	Fish	Fluridone, 4-hydroxy-fluridone	Fluridone, 4-hydroxy-fluridone
Drinking Water		Fluridone, N-methylformamide	Not Applicable

4.0 HAZARD CHARACTERIZATION AND ASSESSMENT

4.1 Hazard Characterization of Fluridone

The Fluridone Toxicity Profile is included in Appendix B and the following is a summary of the effects observed during the toxicology studies.

Acute Effects

The acute toxicity of Fluridone is moderate to low. It is a moderate irritant to the eyes. The acute toxicity values are included in Table 5.

Table 5 - Acute Toxicity of Fluridone			
Guideline	**Study Type**	**Results**	**Tox Category**
81-1	Acute Oral - rat	LD50 >10000 mg/kg	IV
81-2	Acute Dermal - rabbit	LD50 >2000 mg/kg	III
81-381-4	Acute Inhalation - rat	LC50 >2.13 mg/L	IV
81-5	Eye irritation - rabbit	moderate effects*	III
81-6	Dermal irritation - rabbit	no dermal effects	IV
	Dermal sensitization - guinea pig	not sensitizing	N/A
*Slight to moderate corneal dullness, iritis, and conjuctivitis with clearing by 4 days.			

Non-Cancer Toxicity

The results of the subchronic dietary feeding studies showed that fluridone caused increased incidence of hepatic centrilobular hypertrophy in mice and increased absolute and relative liver weights and relative kidney weights in rats. It produced no effects in subchronic dietary feeding study in dogs at 200 mg/kg/day, the highest doses tested. In developmental toxicity studies, maternal toxicity such as increased incidence of abortions and slight decreases in the body weight and food consumption were seen in rabbits at 300 mg/kg/day or above. In the rats, maternal toxicity such as decreased body weight gains and food consumption were seen at 300 mg/kg/day. Developmental toxicity such as decreased fetal weight, increased incidences of rudimentary ribs, and delayed ossification in sternebrae and pelvic girdle were seen at 1000 mg/kg/day.

In a 3-generation reproduction study in rats, no maternal toxicity was seen at any dose levels. Also, the test chemical did not significantly affect any of the reproductive parameters. For the offspring, there was a decreased pup weight on lactation day 2 at 112 mg/kg/day.

In the combined chronic toxicity/carcinogenicity study in rats, chronic toxicity consisted of decreased body weights, decreased eosinophil counts and decreased absolute and relative liver and kidney weights at 81 mg/kg/day. In addition, fluridone at 81 mg/kg/day also caused an increased incidence of small testes, ocular keratitis and pale or granular kidneys.
In a chronic toxicity study in dogs, significant increases in absolute liver weights and increases in alkaline phosphatase activity in female dogs were seen at the highest dose-tested (400 mg/kg/day).

No neurotoxicity was reported in any of the studies.

Mutagenicity and Cancer

Fluridone was negative for inducing mutations in all guideline studies of the standard battery of mutagenicity tests.

In the combined chronic toxicity/carcinogenicity study in rats, there was no treatment-related increase in tumor incidence in any treated groups when compared to controls. The Carcinogenicity study in mice showed no treatment-related increase in tumor incidence in any treated groups when compared to controls. Increase in alkaline phosphatase activity and increased incidence of hepatocellular hyperplasia were seen at 50 mg/kg/day.

The HED Cancer Assessment Review Committee (TXR 007726, July 15 and October 7, 1985) evaluated the available data and concluded that the data did not provide evidence for the carcinogenicity of fluridone in either rats or mice.

4.2 FQPA Hazard Characterization

Adequacy of the Toxicity Data Base

The toxicology database for fluridone is adequate. There are sufficient data available to adequately assess the potential for toxicity to young animals following pre- and/or postnatal exposure to fluridone. These include acceptable developmental toxicity studies in rats and rabbits, as well as a 2-generation reproduction studies in rats.

Evidence of Neurotoxicity

The available database indicated that this chemical does not induce neurotoxicity.

Developmental Toxicity Studies

The developmental toxicity studies in rats and rabbits showed no evidence of additional sensitivity to young rats or rabbits following pre- or postnatal exposure to fluridone and comparable NOAELs were established for adults and offspring.

Reproductive Toxicity Studies

In a 3-generation reproduction study in rats, no maternal toxicity was seen at any dose levels. Also, the test chemical did not significantly affect any of the reproductive parameters. For the offspring, there was a decreased pup weight on lactation day 21 at 112 mg/kg/day.

Additional Information from Literature Sources

A literature search did not find additional neurotoxicity studies or developmental neurotoxicity studies.

Determination of Susceptibility for Pre-and/or post Natal Susceptibility

Prenatal developmental toxicity studies in rats and rabbits provided no indication of increased susceptibility of rat or rabbit fetuses to *in utero* exposure to fluridone. There was indication of increased susceptibility in the offspring as compared to parental animals in the 3-generation reproduction study.

Degree of Concern and Residual Uncertainties for Pre-and/or post-natal Susceptibility

The results of the 3-generation reproduction study in rats showed increased quantitative susceptibility of offspring to fluridone based on reduced pup weight (90.7% controls; $p < 0.05$) on lactation day 21. However, considering the overall toxicity profile and the doses and endpoints selected for risk assessment for fluridone, the degree of concern for the effects observed in this study was considered as low, noting that the study was well-conducted, clear

NOAELs/LOAELs were established, and the dose response for the observed effects are well characterized. In addition, the NOAEL of 8 mg/kg/day identified to established the chronic RfD is more than 4 times less than that of 36 mg/kg/day for offspring toxicity. Therefore, no residual uncertainties were identified for pre- and/or postnatal toxicity.

4.3 Recommendation for a developmental Neurotoxicity Study

The available toxicity data showed no neurotoxicity or offspring toxicity in a reproduction study which would warrant a recommendation for requiring a developmental neurotoxicity study.

4.4 Hazard Identification and Toxicity Endpoint Selection

The toxicity endpoints and doses for fluridone and NMF risk assessment are shown in Tables 6 and 7. The endpoint selected for acute fluridone exposures is conservative because the observed effects (abortions in the rabbit) may not be indicative of a single dose exposure because they occurred late in gestation (between days 20 and 25) in the presence of maternal toxicity. The use of the long term endpoint for short and intermediate term fluridone exposures was done to simplify the risk assessment process. This endpoint is conservative because only minor effects were observed during 90 day studies. These effects include centrilobular hypertrophy and increased liver and kidney weights and they were observed at LOAELs of 25 mg/kg/day in mice and 44 mg/kg/day in rats with NOAELs of 15 mg/kg/day in mice and 25 mg/kg/day in rats.

Table 6 - Endpoints Used for Fluridone Risk Assessment

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Dietary Risk Assessments			
Acute Dietary (Females 13-50 years of age)	Dev. NOAEL = 125 mg/kg/day UF = 100 Acute RfD = 1.25 mg/kg/day	FQPA SF = 1X aPAD = acute RfD / FQPA SF = 1.25mg/kg/day	Developmental Toxicity - Rabbit LOAEL = 300 mg/kg/day based on increased incidences of abortions
Acute Dietary (General population including infants and children)	NOT APPLICABLE. A dose and endpoint were not selected for this population group because there were no effects observed in oral toxicology studies including maternal toxicity in the developmental toxicity studies in rats and rabbits that are attributable to a single exposure (dose).		
Chronic Dietary (All populations)	NOAEL= 15 mg/kg/day UF =100 Chronic RfD = 0.15 mg/kg/day	FQPA SF = 1X cPAD = chronic RfD / FQPA SF = 0.15 mg/kg/day	2 yr cancer study in mice LOAEL =50 mg/kg/day based on increased alkaline phosphatase activity and increased incidence of heptocellular hyperplasia

Table 6 - Endpoints Used for Fluridone Risk Assessment			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Special FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Non-Dietary Risk Assessments			
Short Term Exposures Dermal, Inhalation and Incidental Oral	NOAEL= 15 mg/kg/day MOE = 100	FQPA SF = 1X	2 yr cancer study in mice (Same as above)
Intermediate-Term Exposures - Dermal, Inhalation and Incidental Oral	NOAEL= 15 mg/kg/day MOE =100	FQPA SF = 1X	2 yr cancer study (Same as above)
Long term dermal, Inhalation and Incidental Oral	The endpoint is not applicable because use pattern does not indicate long term exposure.		
Dermal Absorption Factor	39% - Estimated from the ratios of LOAELs from a 21 day dermal toxicity study and a developmental toxicity study in rabbits.		
Cancer	Classification: Not likely to be carcinogenic to humans		

Table 7 - Endpoints Used for NMF Risk Assessment		
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Study and Toxicological Effects**
Acute Oral and Dermal (Females 13-50 years)	Dev. NOAEL = 10 mg/kg/day UF = 100	Developmental Toxicity in Rats and Rabbits[1] - Developmental effects of decreased fetal viability and weight; increased incidence of skeletal malformations with a LOAEL of 75 mg/kg/day for rats and 50 mg/kg/day for rabbits
Acute Oral and Dermal (General population including infants and children)	NOT APPLICABLE. A dose and endpoint were not selected for this population group because there were no effects observed in the developmental toxicity study in rats and rabbits that are attributable to a single exposure (dose).	
Short/Intermediate Term Oral and Dermal	NOAEL= 10 mg/kg/day UF = 100	Developmental Toxicity in Rats and Rabbits[1] - Maternal effects of decreased body weight and food consumption with a LOAEL = 75 mg/kg/day for rats and 50 mg/kg/day for rabbits.
Chronic Oral and Dermal	None	Chronic exposures are not anticipated.
1. Fundamental and Applied Toxicology 27 (2), 239-246, 1995.		

4.5 Special FQPA Safety Factor

The special FQPA Safety Factor can be removed (i.e. 1X) because of the following reasons:

1) acceptable developmental and reproduction studies have been submitted and reviewed;
2) there is no evidence of susceptibility following *in utero* exposure to rats;
3) there is low level of concern and no residual uncertainties for the effects seen in the developmental toxicity study in rabbits and in the 2-generation reproduction studies after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment.

NOTE: The recommended Special FQPA Safety Factor assumes that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

A summary of the FQPA factors for Fluridone is included in Table 8.

Table 8 - Summary of FQPA Safety Factor for Fluridone

	LOAEL to NOAEL (UF_L)	Subchronic to Chronic (UF_S)	Incomplete Database (UF_{DB})	Special FQPA Safety Factor (Hazard and Exposure)
Magnitude of Factor	1X	1X	1X	1X
Rationale for the Factor	No LOAEL to NOAEL extrapolations performed	No subchronic to Chronic extrapolations performed	Database is sufficiently complete to assess risks to infants and children	No residual concerns regarding pre- or post-natal toxicity or completeness of the toxicity or exposure databases
Endpoints to which the Factor is Applied	Not Applicable	Not Applicable	Not Applicable	Not Applicable

4.6 Endocrine Disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program.

the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

In the available toxicity studies on fluridone, there were no estrogen, androgen and/or thyroid mediated toxicity.

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, Fluridone may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

5.0 Public Health Data

6.0 Exposure Characterization and Assessment

6.1 Dietary Exposure and Risk

The dietary exposure assessment is discussed in detail in the Dietary Exposure Assessment Memorandum that was prepared by Christine Olinger (D299947 of June 10,2004). Fluridone acute and chronic dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 1.30), which incorporates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as consumed" (e.g., apple pie) are linked to EPA-defined food commodities (e.g. apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/ARS and EPA. For chronic exposure assessment, consumption data are averaged for the entire U.S. population and within population subgroups, but for acute exposure assessment are retained as individual consumption events. Based on analysis of the 1994-96, 98 CSFII consumption data, which took into account dietary patterns and survey respondents, HED concluded that it is most appropriate to report risk for the following population subgroups: the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, adults 20-49, females 13-49, and adults 50+ years old.

For chronic dietary exposure assessment, an estimate of the residue level in each food or food-form (e.g., orange or orange juice) on the food commodity residue list is multiplied by the average daily consumption estimate for that food/food form to produce a residue intake estimate. The resulting residue intake estimate for each food/food form is summed with the residue intake

estimates for all other food/food forms on the commodity residue list to arrive at the total average estimated exposure. Exposure is expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

For acute exposure assessments, individual one-day food consumption data are used on an individual-by-individual basis. The reported consumption amounts of each food item can be multiplied by a residue point estimate and summed to obtain a total daily pesticide exposure for a deterministic exposure assessment, or "matched" in multiple random pairings with residue values and then summed in a probabilistic assessment. The resulting distribution of exposures is expressed as a percentage of the aPAD on both a user (i.e., only those who reported eating relevant commodities/food forms) and a per-capita (i.e., those who reported eating the relevant commodities as well as those who did not) basis. However, for tiers 1 and 2, any significant differences in user vs. per capita exposure and risk are specifically identified and noted in the risk assessment.

Acute and chronic dietary exposure estimates were also conducted using the Lifeline™ model (Version 2.0). These Lifeline™ assessments were also conducted using the same consumption data as the DEEM-FCID™ (CSFII, 1994-1996 and 1998 consumption data with FCID). Lifeline™ uses the recipe file to relate RACs to foods "as-eaten." Lifeline™ converts the RAC residues into food residues by randomly selecting a RAC residue value from the "user defined" residue distribution (created from the residue, percent crop treated, and processing factors data), and calculating a net residue for that food based on the ingredients' mass contribution to that food item. For example, 'apple pie' will have a residue distribution based on the residues provided for apples (adjusted by the appropriate processing factors and percent crop treated), as well as the residues for each of the other ingredients in the apple pie recipe for which there may be tolerances. Lifeline™ calculates dietary exposure from 'apple pie' based on the amount eaten, and the residue drawn from the 'apple pie' residue distribution for that eating occasion. Lifeline™ models the individual's dietary exposures over a season by selecting a new CSFII diary each day from a set of similar individuals based on age and season attributes. Lifeline™ groups CSFII diaries based on the respondents' age and the season during which the food diary was recorded.

Dietary risk assessment incorporates both exposure and toxicity of a given pesticide. For acute and chronic assessments, the risk is expressed as a percentage of the aPAD or cPAD, respectively. For acute and non-cancer chronic exposures, HED is concerned when estimated dietary risk exceeds 100% of the PAD.

Acute Dietary Exposure and Risk

An unrefined Tier 1 (tolerance level and 100% crop treated(%CT)) acute dietary risk assessment was conducted for fluridone using all existing tolerances. Dietary risk estimates are provided only for females of child-bearing age, because no other acute effects were observed in the oral toxicity studies that are applicable to the general population. At the 95th percentile of exposure,

the acute dietary exposure estimates are below the HED's level of concern (<100% aPAD[1]) for females aged 13-49 years, with the exposure at less than 1% of the aPAD. Similar results were found using the Lifeline model.

Chronic Dietary Exposure and Risk

A Tier 1 assessment, tolerance level residues and the assumption of 100% crop treated, was also conducted for chronic exposure and risk assessment. Chronic dietary exposure and risk were also below HED's level of concern using the DEEM™ and Lifeline™ models, with approximately 1% of the cPAD occupied for the U.S. population. The most highly exposed sub-population were children aged 1-2, with a risk estimate of 3.6 % of the cPAD. These exposures are all well below 100% of the PAD and are not of concern. A summary of the dietary risks are shown in Table 9.

Table 9 - Summary of Dietary Exposure and Risk for Fluridone

Population Subgroup	Dietary Exposure (mg/kg/day)		% PAD [1]	
	DEEM-FCID™	Lifeline™	DEEM-FCID™	Lifeline™
Chronic Assessment				
General U.S. Population	0.001599	0.001514	1.1	1.0
All Infants (< 1 year old)	0.002661	0.002545	1.8	1.7
Children 1-2 years old	**0.005345**	**0.005181**	**3.6**	**3.5**
Children 3-5 years old	0.004123	0.004043	2.7	2.7
Children 6-12 years old	0.002529	0.002339	1.7	1.6
Youth 13-19 years old	0.001454	0.001341	1.0	0.9
Adults 20-49 years old	0.001154	0.001218	0.8	0.8
Adults 50+ years old	0.001074	0.001191	0.7	0.8
Females 13-49 years old	0.001134	0.001377	0.8	0.9
Acute Assessment				
Females 13-49 years old	**0.002352**	**0.003009**	**0.19**	**0.24**

6.2 Water Exposure and Risk

Fluridone is applied directly to water bodies to achieve a target water concentration of 10 ppb to 90 ppb for whole lake treatments and 30 to 150 ppb for partial lake treatments. The target concentration depends upon the flow characteristics of the water body and the species of weed to be controlled. Typically more than one application is made to maintain the target concentration for the required contact time (approximately 45 days), however, the maximum cumulative concentration cannot exceed 150 ppb during the growing season. This means that if the first application is made at 90 ppb the second application can not exceed 60 ppb.

The label contains restrictions regarding fluridone use near potable water intakes. Applications of greater than 20 ppb are not allowed within a quarter mile of intakes while applications of 6 to 20 ppb are allowed at intakes. Given this label restriction it can be assumed that the fluridone EEC for drinking water drawn from lakes would be 20 ppb or less.

The Estimated Environmental Concentrations (EECs) for NMF were derived from the fluridone EECs by assuming a fluridone to NMF conversion efficiency of 74% and by adjusting for the ratio of the fluridone molecular weight of 329 to the NMF molecular weight of 59. The conversion efficiency is the maximum daily value that was observed in an aquatic photolysis study (MRID 419401-04) that was conducted under laboratory conditions using distilled water. Given the above assumptions a fluridone concentration of 20 ug/liter would yield an NMF concentration of 2.64 ug/liter.

Ground Water Modeling

EFED was unable to perform groundwater modeling and recommends the use of the maximum surface water EECs for fluridone (20 ppb) and NMF be used as ground water EECs. For fluridone, adsorption Koc values ranged from 260 to 740 cm^3/g m, indicating medium potential for leaching.

Monitoring Data

EFED has no monitoring data for fluridone or NMF in surface or ground water.

Drinking Water Risk Calculations

The risks of exposure from drinking water were calculated using the EECs from EFED and the following assumptions:

- Body weights (kg) of 70, 60, 10 and 10 were used for adults, adult females, children and infants.
- Water consumption values (liters per day) of 2 , 2, 1 and 1 were used for adults, adult females, children and infants.

Drinking Water MOEs

The MOEs for drinking water exposures are summarized in Tables 10 and 11 and the calculations are included in Appendix B. The fluridone and NMF MOEs exceed the target MOE of 100 by one or more orders of magnitude.

Table 10 - Drinking Water Exposure Fluridone MOEs

Exposed Person - Body Weight	Water Concentration (ug/l)	Water Consumption (liter/day)	Dose (mg/kg/day)	NOAEL (mg/kg/day)	MOE
Acute Exposure					
Adult - 60 kg	20	2	0.00067	125	187500
Short/Intermediate Term and Chronic Exposures					
Adult - 60 kg	20	2	0.00067	15	22500
Adult - 70 kg	20	2	0.00057	15	26250
Infant/Child - 10 kg	20	1	0.00200	15	7500

Table 11 - Drinking Water Exposure NMF MOEs

Exposed Person - Body Weight	Water Concentration (ug/l)	Water Consumption (liter/day)	Dose (mg/kg/day)	NOAEL (mg/kg/day)	MOE
Acute Exposure					
Adult - 60 kg	2.64	2	0.000088	10	113636
Short/Intermediate Term Exposure					
Adult - 70 kg	2.64	2	0.000075	10	132576
Infant/Child - 10 kg	2.64	1	0.000264	10	37879

6.3 Residential Exposure/Risk Pathway

Recreational Swimmer Exposures and Risks

There is a possibility that swimmer exposure could occur following fluridone applications because these applications are often made at recreational lakes To address the risks of these exposures, the SWIMODEL was used with the following assumptions.

* The skin surface area of adults is assumed to be 21,000 cm^2 as cited in the Residential SOPs. This is the 95th percentile value for females (EPA Exposure Factors Handbook. 1997).
- The body weight for children is assumed to be 22 kg as cited in the Residential SOPs. This is a mean value for 6 year old children.
- The skin surface area for children is assumed to be 9,000 cm^2 as cited in the Residential SOPs. This is the 90th percentile value for male and female children.
- The assumed mean ingestion rate is 0.05 liters per hour for both adults and children as cited in the Residential SOP. This value may be greater for young children playing in water and accidentally ingesting a remarkable quantity of water (U.S. EPA SAP. 1999).
- The exposure time is assumed to be 3 hours per day. This is the 90th percentile value for time spent swimming in a freshwater pool. (EPA Child Specific Exposure Factors Handbook, 2002).
- The body weight for adult acute exposure is assumed to be 60 kg because the endpoint is gender specific.
- The body weight for adult short and intermediate term exposures is assumed to be 70 kg because the endpoint are not gender specific.
- The maximum label application rate of 0.15 mg/liter (150 ppb) was used to assess acute and short/intermediate term fluridone exposures.
- A concentration of 0.020 mg/liter (20 ppb) was used to assess the acute and short term NMF exposures. This concentration was derived from the fluridone concentration of 150 ppb by assuming a fluridone to NMF conversion rate of 74% and adjusting for molecular weight.

Calculation Methods

The above factors were used in the SWIMODEL formulae for the dermal, ingestion, aural. buccal/sublingual and nasal/orbital routes of exposure.

Results

The MOEs for recreational swimmers are summarized in Tables 12 and 13 and the calculations are included in Appendix C. The fluridone and NMF MOEs exceed the target MOE of 100 by one or more orders of magnitude.

Table 12 - Recreational Swimmer Fluridone MOEs					
Exposed Person	**Exposure Duration**	**Water Concentration (ug/l)**	**Dose (mg/kg/day)**	**NOAEL (mg/kg/day)**	**MOE**
Adult - 60 kg	Acute	150	0.0012	125	100,000
Adult - 60 kg	Short/Intermediate Term	150	N/A	N/A	N/A
Adult - 70 kg		150	0.0010	15	15,000
Child - 22 kg		150	0.0031	15	4,800

Table 13 - Recreational Swimmer NMF MOEs					
Exposed Person	**Exposure Duration**	**Water Concentration (ug/l)**	**Dose (mg/kg/day)**	**NOAEL (mg/kg/day)**	**MOE**
Adult - 60 kg	Acute	20	0.00015	10	66,000
Adult - 60 kg	Short/ Intermediate Term	20	N/A	N/A	N/A
Adult - 70 kg		20	0.00013	10	77,000
Child - 22 kg		20	0.00040	10	24,000

Other Residential Exposures

Spray drift

Liquid applications of fluridone are made via subsurface injection while aerial applications are made only with granular materials. These methods of application have a relatively low drift potential. In addition, is unlikely that drift exposures would exceed the swimmer exposures because fluridone is applied directly to water bodies.

7.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

In examining aggregate exposure, FQPA directs EPA to take into account available information concerning exposures from pesticide residues in food and other exposures for which there is reliable information. Although fluridone is not a food use chemical, fluridone residues may be present in fish harvested from fluridone treated waters or in crops irrigated with fluridone treated water. Aggregate risks have been calculated for Fluridone and the degradate N-methyl Formamide (NMF) There are residential (recreational swimmer) exposures to Fluridone and NMF; therefore, the considerations for aggregate exposure are those from food, drinking water and residential exposure.

7.1 Aggregate Risk Assessment for Fluridone

The aggregate risks were calculated for the various fluridone exposure durations and populations by adding the applicable exposures scenarios and comparing the aggregate doses to the appropriate fluridone endpoints. Body weights of 70, 60, 10 and 10 kg were used for adults, adult females, children and infants, respectively. The acute aggregate risks were calculated only for females because the acute NOAEL is based upon developmental effects and only applies to females. Short and intermediate term aggregate risk were calculated based on chronic food exposure plus the swimmer exposure for adults and children 1 to 6 and based upon the chronic food exposure only for infants. Long term aggregate risks were calculated based on food exposure only because the swimmer exposure does occurs on long term basis. All of the aggregate MOEs exceed the target MOE of 100 by one or more orders of magnitude which means that the aggregate risks are not of concern. A listing of the fluridone aggregate MOEs is included in Table 14.

Table 14 - Fluridone Aggregate MOEs

Population Subgroup	Exposure Duration	Food Exposure (mg/kg/day)	Swimmer Exposure (mg/kg/day)	Drinking Water Exposure (mg/kg/day)	Aggregate Exposure[A] (mg/kg/day)	NOAEL (mg/kg/day)	Aggregate MOE[B]
Females 13-49 yrs	Acute	0.0030	0.0012	0.00067	0.0049	125	25667
U.S. Population	Short/ Intermediate Term	0.0016	0.0010	0.00057	0.0032	15	4732
Children 1-6 yr		0.0044	0.0031	0.00200	0.0095	15	1579
All Infants		0.0027	N/A	0.00200	0.0047	15	3191
U.S. Population	Long Term	0.0016	N/A	0.00057	0.0022	15	6912
Females 13-50 yrs		0.0013	N/A	0.00067	0.0020	15	7614
Children 1-6 yr		0.0044	N/A	0.00200	0.0064	15	2344
All Infants		0.0027	N/A	0.00200	0.0047	15	3191

A. Aggregate Exposure = Swimmer Exposure + Drinking Water Exposure + Drinking Water Exposure
B. Aggregate MOE = NOAEL/Aggregate Exposure

7.2 Aggregate Risk Assessment for NMF

The aggregate risks were calculated for drinking water and swimmer exposure only because NMF is not found in foods. The acute risks were calculated only for females because the acute NOAEL is based upon developmental effects and only applies to females. Short term risks were calculated based the swimmer exposure for adults and children 1 to 6 and based upon the drinking water exposure only for infants. All of the aggregate MOEs exceed the target MOE of 100 by one or more orders of magnitude which means that the aggregate risks are not of concern. A listing of the NMF aggregate MOEs is included in Table 15.

Table 15 - NMF Aggregate MOEs

Population Subgroup	Exposure Duration	Swimmer Exposure (mg/kg/day)	Drinking Water Exposure (mg/kg/day)	Aggregate Exposure[A] (mg/kg/day)	NOAEL (mg/kg/day)	Aggregate MOE[B]
Females 13-50 yrs	Acute	0.00015	0.00067	0.00082	10	12245
U.S. Population	Short/ Intermediate Term	0.00013	0.00057	0.00070	10	14257
Children 1-6 yr		0.00041	0.00200	0.00241	10	4149
All Infants		N/A	0.00200	0.00200	10	5000

A. Aggregate Exposure = Swimmer Exposure + Drinking Water Exposure
B. Aggregate MOE = NOAEL/Aggregate Exposure

7.3 Risk Characterization

This risk assessment was based upon the assumption that maximum label rates of 90 to 150 ppb would be used. Literature data and discussions with the aquatic plant management community have indicated, however, that actual use rates are in the range of 10 to 20 ppb due to the high cost of fluridone and it's proven efficacy at these lower rates.

The use of the aural, buccal/sublingual and nasal/orbital components of the swim model are conservative because these components are based upon head immersion which is less likely to occur for significant time periods during recreational lake swimming. In addition the buccal/sublingual and nasal/orbital components of the swim model use an absorption rate of 1 percent (of the chemical dissolved in the water) which is based upon the rate of sublingual absorption of nitroglycerin. Nitroglycerin is rapidly absorbed through the skin and mucous membranes and for this reason it is administered sublingually for the rapid relief of angina.

8.0 Cumulative Risk

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to fluridone and any other substances and fluridone does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that fluridone has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

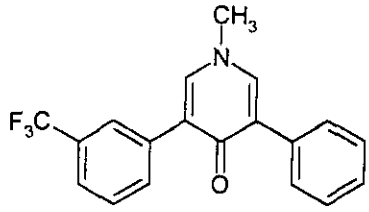
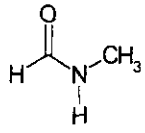
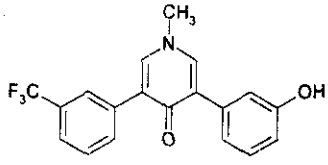
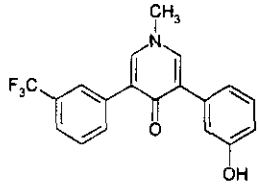
9.0 Data Gaps and Label Requirements

Toxicology

No data gaps have been identified.

Residue Chemistry

No data gaps have been identified.

Appendix A - Summary of Fluridone Metabolites and Degradates				
Chemical Name	Commodity	Percent TRR [1]		Structure
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)	
Fluridone	Irrigated Crops [2]	73-90%		
	Ruminant		liver 1.8%	
	Swine		liver 0.2%	
	Rat	Excreta 60% max		
	Bluegill	61%		
	Water			
N-Methyl Formamide	Water	74% max		
2-hydroxy-Fluridone	Bluegill		1.7%	
4-hydroxy-Fluridone	Bluegill	10%		
	Ruminant		liver 2%	
	Swine		liver 0.4%	
	Rat [3]		excreta 2.4% max	
3-CF_3-benzoic acid	Water	29% max		
benzoic acid	Water	14.6% max		
3-CF_3-benzaldehyde	Water		<0.4%	
benzaldehyde	Water		<0.5%	

Appendix A - Summary of Fluridone Metabolites and Degradates				
Chemical Name	Commodity	Percent TRR [1]		Structure
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)	

[1] Results are reported as percent of the total radioactive residue (TRR) from the metabolism studies. Maximum levels from laboratory environmental fate studies are reported as percent of applied dose.

[2] Irrigated crop studies were conducted on grapefruit, lettuce, soybean, corn, and alfalfa.

[3] The rat metabolism data have not been reviewed by HED. No other rat metabolites identified in the excreta exceeded 10% of the administered dose, with the exception of the total of four isomeric forms of a polar metabolite tat ranged from 4.34-19.56% of the applied dose. This metabolite retains the three ring structure, but has lost the trifluromethyl group and is extensively hydroxylated.

Note: Metabolism studies were also conducted on cotton (as a direct treatment) and poultry. TRRs were very low and no characterization of residues was conducted. In addition no characterization of residues was done in the lactating cow, steer, and swine metabolism studies on any matrix but liver as radioactivity levels were very low or non-detectable.

Appendix B - Fluridone Toxicity Profile (Subchronic, Chronic and Other)				
DER #	**STUDY TYPE– DOSE LEVELS**	**NOAEL mg/kg/day**	**LOAEL mg/kg/day**	**EFFECTS**
1	2-year combined chronic/carcinogenicity (1980) –RAT 0, 200, 650, 2000 ppm for 2 years (0,7.65, 25.15, 80.8 mg/kg/day in males and 9.17, 30.11, 97.00 mg/kg/day in females) MRID 103305 and 103251	7.65 ADI = 8 mg/kg/d	25.15	↓ body weights (92% of controls; $p<0.05$) ↑ absolute and relative liver and kidney weights Treatment related increase in tumor incidence was not found. At 80.8 mg/kg/day (HDT) ↑ mortality (87% in ♂; 37% in ♀) ↑ chromorhinorrhea, anorexia, cloudy eyes, pale eyes ↓ body weight (59-66% in ♂; 81-89% in ♀) ↓ food consumption ↓ RBC counts, Hb, hematocrit, MCV, MCH ↓ lymphocyte and eosinophil counts ↑ nucleated erythrocytes, leukocyte and neutrophil counts ↑ total leukocyte count ↑ BUN, creatinine, bilirubin ↑ small testes, dose-related trends in number of enlarged, pale and/or granular kidneys; opaque, cloudy, pale, red, or ulcerated eyes; and skin nodules or masses. ↑ absolute and relative liver and kidney weights ↑ atrophy of testes, ocular keratitis, epidermal inclusion cyst
2	2-year carcinogenicity –mouse (1981-1982) 0, 33, 100, or 330 ppm for 2 years (equivalent to 0, 5, 15 or 50 mg/kg/day) MRID No.103252 & 103335	15	50	↑alkaline phosphatase activity (209% of controls) ↑ incidence of hepatocellular hyperplasia (2, 2, 4, and 6 cases in control, low-, mid-, and high-doses) Treatment related increase in tumor incidence was not found.
3	1-year chronic study in dog (1981) of 0, 75, 150, or 400 mg/kg/day MRID No. 103336	150	400	↑ absolute liver weights ↑ alkaline phosphatase activity (in female dogs)
4	Developmental toxicity–rats (1986) CD rats 0, 100, 300, or 1000 mg/kg/day by oral gavage on gestation days 6 through 15 inclusive MRID 159963	maternal 100 developmental 300	maternal 300 developmental 1000	↓ body weight gain and food consumption ↓ fetal body weight, ↑ rudimentary ribs ↑ delayed ossification in sternebrae and pelvic girdle

Appendix B - Fluridone Toxicity Profile (Subchronic, Chronic and Other)

DER #	STUDY TYPE– DOSE LEVELS	NOAEL mg/kg/day	LOAEL mg/kg/day	EFFECTS
5	Developmental toxicity–rabbits (1980) Dutch Belted rabbits (15/sex/dose) on days 6-18 of gestation at dose levels of 0, 125, 300, or 750 mg/kg/day MRID 103302	maternal 125 developmental 125	maternal 300 developmental 300	↓ body weight and food consumption ↑ incidences of abortions (4/14 aborted between days 20 and 25 of gestation) ↑ incidences of abortions (see above) At 750 mg/kg/day, 6/11 aborted between days 20 and 25 of gestation
6	3-generation reproduction study—rat (1980) 0, 200, 650, or 2000 ppm. calculated intake of fluridone during the growth phases over the 3 generations were 10.6-11.1, 35.5-36.6, or 111.9-112.3 mg/kg/day for males and 12.4-13.2, 40.4-44, or 128-131.4 mg/kg/day for females. MRID 103304	parental toxicity >112, HDT offspring toxicity 36 Reproductive toxicity >112, HDT Developmental toxicity >112, HDT	parental toxicity >112 offspring toxicity 112 Reproductive toxicity >112 Developmental toxicity >112	↓ pup weight (90.7% of controls; $p<0.05$; on lactation day 21)
7a	Metabolism study–RAT (1981) ^{14}C-labeled Fluridone (^{14}C labeled in the 4-position of the pyridinone ring) 10, 100, 250, 500 or 1000 mg/kg MRID 103261 & 103262			Readily absorbed and eliminated. Total recovery of dosed radioactivity = 78-90% (3 days) 4-19 % (urine) 68-85 % (feces) Negligible% (tissues and carcasses) 66% (bile) Component in urine and feces–not identified Major component (37% of dose) in bile–not identified Minor component in bile: Fluridone (8% of dose) 4-hydroxyphenyl fluridone (6% of dose)

Appendix B - Fluridone Toxicity Profile (Subchronic, Chronic and Other)				
DER #	**STUDY TYPE– DOSE LEVELS**	**NOAEL mg/kg/day**	**LOAEL mg/kg/day**	**EFFECTS**
7b	Metabolism study–RAT (1997) ^{14}C-labeled Fluridone 10 or 1000 mg/kg MRID 44265101			Eight (8) metabolites were identified from feces. Fluridone was extensively metabolized primarily through ring hydroxylation and N-demethylation.
8	21-Day Dermal Toxicity - Rabbit (1981) 0, 192, 384 or 768 mg/kg/day for 21 days (6 hours/day and 5 days/week). MRID No. 103299	systemic 384 dermal toxicity lower than 192 (LDT)	systemic 768 dermal toxicity lower than 192 (LDT)	decreased relative kidney weights (85% of controls, $p<0.05$) transient, slight erythema in 9/10 animals accompanied by slight desquamation at 192 mg/kg (LDT)
9	90-day oral toxicity-mice (1978) 0, 62, 110, 200, 330, or 560 ppm (equivalent to 0, 9.3, 16.5, 30, 49.5 or 84 mg/kg/day based on 1 ppm = 0.15 mg/kg/day) MRID 82342 NOTE: 50% of the theoretical concentration was present in the feed sample after 3 months storage. Therefore, corrected doses administered are 4.6, 8.3, 15, 25, and 42 mg/kg/day.	15 –see note under study type	25 –see note under study type	↑ centrilobular hypertrophy of the liver (incidences of centrilobular hypertrophy of the liver were 0/30, 1/28, 2/29, 3/29, and 6/30 cases in control, low-, mid-, high- and highest-doses) NOTE: The dose related findings of this lesion was also observed in other 90-day mouse study with fluridone (MRID No. 82341
10	90-day oral toxicity-rat (1978) 0, 330, 560, 1000, 1400, or 2000 ppm (males: 0, 30, 54, 106, 139, or 178.4; females: 0, 34, 53, 94, 126, or 202 mg/kg/day based on initial food consumption) MRID 135209 NOTE: 81.9% of the theoretical concentration was present in the feed sample after 1 week storage. Therefore, corrected doses administered are 25, 44, 87, 114, or 146 m/k/d for males.	25 –see note under study type	44 –see note under study type	↑ absolute and relative liver (112-113% of controls) and relative kidney weights (106% of controls) (males only) In males at 2 highest doses (114 and 146 m/k/d) ↑ centrilobular hypertrophy of the liver (1/15 of 114 m/k/d group) (12/15 of 146 m/k/d group)
11	90-day oral toxicity-dog (1978) 0, 50, 100, or 200 mg/kg/day (oral capsules) MRID: 82344	>250 (HDT)	not established	
12	dermal absorption rat			not available

Appendix B - Fluridone Toxicity Profile (Subchronic, Chronic and Other)				
DER #	**STUDY TYPE– DOSE LEVELS**	**NOAEL mg/kg/day**	**LOAEL mg/kg/day**	**EFFECTS**
13	Microbial mutagenicity assay (Ames assay) MRID 255339			not mutagenic
14	*In Vivo* Mammalian Cytogenetics - Sister Chromatid Exchange assay in Chinese hamsters MRID 070942			Not mutagenic
15	Unscheduled DNA damage/repair MRID 070942			Not mutagenic
16	Unscheduled DNA damage/repair MRID 070942			Not mutagenic

Appendix C - Recreational Swimmer Risks in Aquatic Areas Treated With Fluridone
Spreadsheet C1: Fluridone Exposures

Dermal Exposure

Exposed Person	Fluridone Water Concentration (mg/l)	Exposed Surface Area (cm2)	Exposure Time (Hours/day)	Kp (cm/hr)		Conversion factor (L/1000 cm3)	Absorbed Dose (mg/kg/BW)	Acute MOE	ST MOE
Adult - 60 kg	0.15	21000	3	0.00040		0.001	6.3E-005	1984127	N/A
Adult - 70 kg	0.15	21000	3	0.00040		0.001	5.4E-005	N/A	277778
Child - 22 kg	0.15	9000	3	0.00040		0.001	7.4E-005	N/A	203704

Ingestion Exposure

Exposed Person	Fluridone Water Concentration (mg/l)	Ingestion Rate(L/hr)	Exposure Time (Hours/day)				Absorbed Dose (mg/kg/BW)	Acute MOE	ST MOE
Adult - 60 kg	0.15	0.05	3				3.8E-004	333333	N/A
Adult - 70 kg	0.15	0.05	3				3.2E-004	N/A	46667
Child - 22 kg	0.15	0.05	3				1.0E-003	N/A	14667

Aural Exposure

Exposed Person	Fluridone Water Concentration (mg/l)	Exposed Surface Area (cm2)	Exposure Time (Hours/day)	Kp (cm/hr)	Kow	Conversion factor (L/1000 cm3)	Absorbed Dose (mg/kg/BW)	Acute MOE	ST MOE
Adult - 60 kg	0.15	4	3	0.00040	74.1	0.001	8.9E-007	1.4E+008	N/A
Adult - 70 kg	0.15	4	3	0.00040	74.1	0.001	7.6E-007	N/A	2.0E+007
Child - 22 kg	0.15	4	3	0.00040	74.1	0.001	2.4E-006	N/A	6.2E+006

Buccal/Sublingual Exposure

Exposed Person	Fluridone Water Concentration (mg/l)	Water Intake Rate(L/hr)	Exposure Time (Hours/day)	Absorption Rate			Absorbed Dose (mg/kg/BW)	Acute MOE	ST MOE
Adult - 60 kg	0.15	5	3	0.01			3.8E-004	333333	N/A
Adult - 70 kg	0.15	5	3	0.01			3.2E-004	N/A	46667
Child - 22 kg	0.15	5	3	0.01			1.0E-003	N/A	14667

Nasal/Orbital Exposure

Exposed Person	Fluridone Water Concentration (mg/l)	Water Intake Rate(L/hr)	Exposure Time (Hours/day)	Absorption Rate			Absorbed Dose (mg/kg/BW)	Acute MOE	ST MOE
Adult - 60 kg	0.15	5	3	0.01			3.8E-004	333333	N/A
Adult - 70 kg	0.15	5	3	0.01			3.2E-004	N/A	46667
Child - 22 kg	0.15	5	3	0.01			1.0E-003	N/A	14667

Combined Exposure

Exposed Person	Acute Dose (mg/kg/BW)	Acute MOE	ST Dose (mg/kg/BW)	ST MOE					
Adult - 60 kg	0.0012	105140	N/A	N/A					
Adult - 70 kg		N/A	0.0010	14720					
Child - 22 kg		N/A	0.0031	4771					

Notes

KOW value of 74.1 is from ARS Database

KP value is calculated from MW and KOW using swim model formula.

NOAEL = 125 mg/kg/day for acute exposures (females 13 to 50 only)

NOAEL = 15 mg/kg/day for short/intermediate term exposures (All other adults and children)

Appendix C - Recreational Swimmers Risks in Aquatic Areas Treated With Fluridone
Spreadsheet C2: NMF Exposures

Dermal Exposure

Exposed Person	NMF Water Concentration (mg/l)	Exposed Surface Area (cm2)	Exposure Time (Hours/day)	Kp (cm/hr)			Conversion factor (L/1000 cm3)	Absorbed Dose (mg/kg/BW)	Acute MOE	ST MOE
Adult - 60 kg	0.0198	21000	3	0.00017			0.001	3.6E-006	2764371	N/A
Adult - 70 kg	0.0198	21000	3	0.00017			0.001	3.1E-006	3225099	3225099
Child - 22 kg	0.0198	9000	3	0.00017			0.001	4.2E-006	2365073	2365073

Ingestion Exposure

Exposed Person	NMF Water Concentation (mg/l)	Ingestion Rate(L/hr)	Exposure Time (Hours/day)					Absorbed Dose (mg/kg/BW)	Acute MOE	ST MOE
Adult - 60 kg	0.0198	0.05	3					5.0E-005	202020	N/A
Adult - 70 kg	0.0198	0.05	3					4.2E-005	N/A	235690
Child - 22 kg	0.0198	0.05	3					1.4E-004	N/A	74074

Aural Exposure

Exposed Person	NMF Water Concentation (mg/l)	Exposed Surface Area (cm2)	Exposure Time (Hours/day)	Kp (cm/hr)	Kow		Conversion factor (L/1000 cm3)	Absorbed Dose (mg/kg/BW)	Acute MOE	ST MOE
Adult - 60 kg	0.0198	4	3	0.00017	0.11		0.001	7.6E-011	1.3E+011	N/A
Adult - 70 kg	0.0198	4	3	0.00017	0.11		0.001	6.5E-011	N/A	1.5E+011
Child - 22 kg	0.0198	4	3	0.00017	0.11		0.001	2.1E-010	N/A	4.8E+010

Buccal/Sublingual Exposure

Exposed Person	NMF Water Concentation (mg/l)	Water Intake Rate(L/hr)	Exposure Time (Hours/day)	Absorption Rate				Absorbed Dose (mg/kg/BW)	Acute MOE	ST MOE
Adult - 60 kg	0.0198	5	3	0.01				5.0E-005	202020	N/A
Adult - 70 kg	0.0198	5	3	0.01				4.2E-005	N/A	235690
Child - 22 kg	0.0198	5	3	0.01				1.4E-004	N/A	74074

Nasal/Orbital Exposure

Exposed Person	NMF Water Concentation (mg/l)	Water Intake Rate(L/hr)	Exposure Time (Hours/day)	Absorption Rate				Absorbed Dose (mg/kg/BW)	Acute MOE	ST MOE
Adult - 60 kg	0.0198	5	3	0.01				5.0E-005	202020	N/A
Adult - 70 kg	0.0198	5	3	0.01				4.2E-005	N/A	235690
Child - 22 kg	0.0198	5	3	0.01				1.4E-004	N/A	74074

Combined Exposure

Exposed Person	Acute Dose (mg/kg/BW)	Acute Combined MOE	ST Dose (mg/kg/BW)	ST Combined MOE						
Adult - 60 kg	0.00015	65739	0.00015	N/A						
Adult - 70 kg	N/A	N/A	0.00013	76695						
Child - 22 kg	N/A	N/A	0.00041	24436						

Notes

KOW value is from TOXNET HSDB (antilog of -0.97).

KP value is calculated from MW and KOW using swim model formula.

NOAEL = 10 mg/kg/day for acute exposures (females 13 to 50 only) and short term exposures (all other adults and children)

13544

R105425

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